



# An overview of nine clinical trials of salmeterol in an asthmatic population

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In an attempt to establish the protection afforded by regular salmeterol use against induced bronchoconstriction in asthmatic patients, a meta-analysis was conducted on nine double-blind clinical trials that fulfilled the inclusion criteria.

In each trial, subjects were randomly assigned to receive either salmeterol 50 µg twice daily or a comparator (placebo or salbutamol). Two hundred and twenty-five asthmatic subjects had at least one PC<sub>20</sub> or PD<sub>20</sub> (histamine or methacholine concentration or dose producing 20% fall in forced expiratory volume in 1 s) measurement recorded within 1 h to 16 weeks after the first dose, and up to 31 days after the last dose, of medication.

One hour after the first dose of salmeterol, there was a 3.5-fold increase in doubling dose compared to baseline. Within 12 h of the first dose, the level of protection was 1.5 doubling doses, and protection was maintained at 0.5-1.5 doubling doses over 16 weeks' treatment. This level of protection was maintained for up to 60 h after the last dose. At no time during the washout period did the level of protection fall below zero. Salmeterol afforded significantly greater protection at all time points during the treatment period than comparator agents, but there was no significant difference during the washout period.

In conclusion, salmeterol affords protection against bronchoconstrictor stimuli, and any reduction in this bronchoprotective effect occurred during the first few days of treatment. During long-term salmeterol treatment, there was maintained significant protection that showed no evidence of attenuation after 16 weeks' treatment. Furthermore, there was no evidence of rebound deterioration in bronchial responsiveness after cessation of salmeterol treatment.

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## Introduction

Asthma is a chronic disease that manifests itself as episodic dyspnoea, wheezing and cough. Pathophysiologically, asthma is characterized by variable airway obstruction that is associated with an exaggerated response to various bronchoconstrictor stimuli (1). This airway hyper-responsiveness takes the form of increases in both the sensitivity and the maximal response of the airways to stimuli such as inhaled histamine or methacholine (2). Irrespective of the stimulant triggering bronchoconstriction, in most situations the pathophysiological end response is an increase in airway cell inflammatory burden. As a result, current therapeutic guidelines for the management of asthma are directed against the inflammatory process by using inhaled corticosteroids. For symptom relief, intermittent use of short-acting  $\beta_2$ -agonists is recommended (3).

Recently, two long-acting  $\beta_2$ -agonists, salmeterol and formoterol, have become available. Salmeterol has been

shown to increase morning and evening peak flow, reduce diurnal variations in peak flow, alleviate the symptoms of asthma and reduce the requirement for additional bronchodilator therapy (4,5). The bronchodilator activity of salmeterol lasts for up to 12 h, whereas conventional  $\beta_2$ -agonists are effective for only 4-5 h (6,7). Thus, salmeterol, administered at a dose of 50 µg twice daily from a metered-dose inhaler or in powder form, has been shown to be an effective long-acting bronchodilator for the management of asthma symptoms. A similar long duration of action has been shown for its protective effects against bronchoconstrictor stimuli such as inhaled histamine (8), methacholine (9), allergen (10), hyperventilation with dry cold air (11) and exercise (12). In addition, salmeterol has been shown to decrease the activity of eosinophils in bronchoalveolar lavage fluid (13), and *in vitro* salmeterol has been reported to inhibit inflammatory mediator release from sensitized human lung tissue and from stimulated alveolar macrophages (14,15). These results indicate that long-term treatment with salmeterol could have beneficial effects on airway hyper-responsiveness in asthma.

A variety of studies have examined the protection afforded by the long-term use of salmeterol against

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TABLE 1. Summary of the nine trials used in this meta-analysis

Trial no.	Age	No. of subjects	Trial design	Comparator	Treatment duration	Reference
1	Adults	24	Parallel	Placebo	8 weeks	19
2	Adults	19	Parallel	Placebo	8 weeks	17
3	Adults	12	Crossover	Placebo	4 weeks	13
4	Adults	19	Parallel	Salbutamol	6 weeks	16
5	Children	30	Parallel	Salbutamol	16 weeks	23
6	Adults	22	Parallel	Placebo	6 weeks	22
7	Adults	34	Parallel	Placebo	8 weeks	18
8	Children	40	Parallel	Placebo	16 weeks	21
9	Children	25	Parallel	Salbutamol	6 weeks	20

histamine- or methacholine-induced bronchoconstriction, and whether tolerance develops to this effect. The aim of this meta-analysis was to use nine of these studies (13,16–23), which met pre-defined inclusion criteria, to establish the level of maintained protection afforded by long-term regular use of salmeterol against histamine- or methacholine-induced bronchoconstriction, and to assess bronchial reactivity following withdrawal of long-term salmeterol therapy.

## Methods

Nine double-blind clinical trials performed before December 1994 by Glaxo Research and Development, in which a total of 225 asthmatic patients (adults and children) were randomly assigned to receive either salmeterol 50 µg twice daily or a comparator, were combined in a meta-analysis to establish the protection afforded by regular salmeterol use against histamine- or methacholine-induced bronchoconstriction. Inclusion criteria were: double-blind, randomized trial of either parallel or crossover design, of at least 4 weeks duration; patients receiving long-term salmeterol 50 µg twice daily in one of the treatment arms; and at least one assessment of bronchial reactivity to histamine or methacholine challenge during the trial. Table 1 summarizes the nine trials according to the trial design, patient, sample size, age group, duration of treatment and comparator drug.

In eight of the trials, subjects entered a double-blind parallel treatment period and were randomly allocated, in equal numbers, to either salmeterol 50 µg twice daily or a comparator treatment (either placebo or salbutamol). Trial 3 was of a double-blind crossover design, with subjects randomly assigned to either salmeterol or placebo for a 4-week period, before receiving the alternative treatment for a further 4 weeks. Only data for the first period of the trial was used in the meta-analysis. Trial 9 consisted of two phases, the first of which adopted a crossover design in which patients were randomly allocated to salmeterol 25 or 50 µg, or placebo, to compare the duration of action of salmeterol and to examine the safety of inhaled salmeterol when used prophylactically

before physical activity in children with exercise-induced asthma. In the second phase, subjects were randomly allocated to either salmeterol 50 µg twice daily, or salbutamol 200 µg twice daily, in a 6-week parallel trial. Only data from this latter phase of the trial were used in the meta-analysis.

## Analysis

To combine the nine trials for the meta-analysis, the effect of treatment on each patients was measured by the doubling dose change, which was defined for each visit ( $DD_{\text{visit}}$ ), as:

$$DD_{\text{visit}} = \log_{10}(\text{PC}_{20} \text{ or } \text{PD}_{20} \text{ at visit}) - \log_{10}(\text{PC}_{20} \text{ or } \text{PD}_{20} \text{ at baseline}) / \log_{10} 2$$

where  $\text{PC}_{20}$  was defined as the concentration of histamine or methacholine that produced a 20% fall in forced expiratory volume in 1 s ( $\text{FEV}_1$ ), and  $\text{PD}_{20}$  was defined as the dose of histamine or methacholine that produced a 20% fall in  $\text{FEV}_1$ . In each study, either the  $\text{PC}_{20}$  or the  $\text{PD}_{20}$  values were recorded for the duration of the trial.

Measurements of  $\text{PC}_{20}$  and  $\text{PD}_{20}$  were recorded within 1 h to 16 weeks after the first dose of medication, and up to 31 days after the last dose of medication. However, the number and scheduling of patient visits was not consistent over the nine trials. In trial 4, a study designed to evaluate the short-term rebound deterioration in airway responsiveness following cessation of treatment,  $\text{PD}_{20}$  values were recorded three times during the washout period (24 h, 72 h and 2 weeks after the last dose of medication) but never during treatment. In contrast, subjects in trials 3 and 7 had at least one  $\text{PC}_{20}$  or  $\text{PD}_{20}$  value recorded during the treatment period but not during the washout period. In all other studies,  $\text{PC}_{20}$  or  $\text{PD}_{20}$  values were recorded at least once during both the treatment and washout periods. In trial 8, the  $\text{PC}_{20}$  value was measured at 4 pm and 4 am at baseline and after 16 weeks' treatment, and the  $\text{PC}_{20}$  value at 4 pm was measured after 8 h, 1 week and 8 weeks. Measurements were also recorded at 8 am and 4 pm within 24 h of completion of treatment, and against at 4 pm 1 week

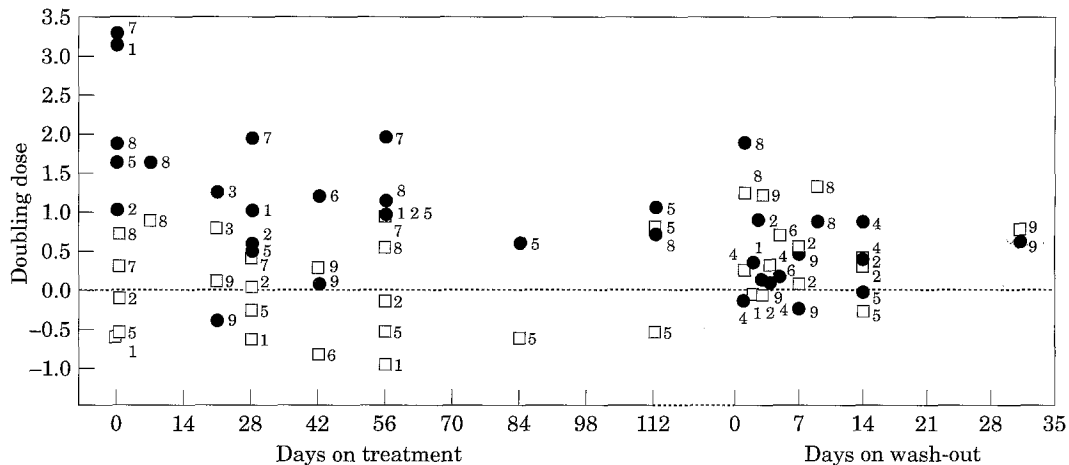


FIG. 1. Mean change in doubling dose during treatment and washout periods for salmeterol (●) and comparator (□) drug. Numbers indicates trial number (see Table 1).

later. Only the measurements taken at 4 pm were used in the meta-analysis.

The meta-analysis examined the difference between the treatment groups over five time intervals: up to 1 h after the first administered dose; between 1 and 12 h after the first dose; during treatment; up to 60 h after the last administered dose (early washout); and more than 60 h after the last administered dose (late washout). Measurement during the 'on treatment' interval consisted of those recorded at, or before, 8 weeks of trial treatment but at least 12 h after commencing treatment; the latest measurement available in this time interval was considered for the analysis. No measurements taken later than 8 weeks after commencing treatment were used for this grouping. Similarly, the latest measurement available up to 14 days, but not before 60 h, of ceasing treatment was taken for the 'more than 60 h after last dose' group.

Information for each of time interval was pooled from the individual trials using the equations:

$$\tau = \frac{\sum w_i \tau_i}{\sum w_i^2 \sigma_i^2}$$

where  $\tau_i$  represents the difference in the mean doubling dose between salmeterol and comparator agent for trial  $i$ ,  $\tau$  is the overall weighted mean effect size,  $\sigma_i^2$  is the variance of the estimated mean difference and  $w_i$  is the weight used for trial  $i$  subject to the condition that  $\sum w_i = 1$ . The 100(1- $\alpha$ )% confidence interval (C) for the overall weighted mean effect in each time interval is then given by:

$$\tau \pm C_{\alpha/2} \sqrt{\text{Var}(\tau)}$$

where  $C_{\alpha/2}$  is the two-tailed critical value of the standard normal distribution.

This method of pooling assumes that each of the treatment estimates may be regarded as being normally distributed with known variance,  $\text{Var}(\tau)$ . In this analysis, equal weighting per trial is used, i.e.  $w = 1/n$ , where  $n$  is the number of trials at the relevant timepoint.

## Results

The mean changes in doubling dose (from baseline) during the various treatment and washout periods for each trial are shown in Fig. 1. The combined mean doubling dose values at each timepoint for salmeterol and comparator drug during the treatment and the washout periods are shown in Fig. 2. Salmeterol had a protective effect on airway reactivity to bronchoconstrictor stimuli, as indicated by a positive doubling dose value (i.e. an increase in  $\text{PC}_{20}$  or  $\text{PD}_{20}$  value on treatment compared to baseline). One hour after the first dose, the protective effect of salmeterol was approximately 3.5 doubling doses. Within 12 h of the first dose, the level of protection was 1.5 doubling doses, with a maintained level of protection between 0.5 and 1.5 doubling doses that persisted for 16 weeks of treatment. Furthermore, salmeterol had a protective effect for up to 60 h after the last dose. At no time during the washout period did the level of protection fall below zero, thus showing no evidence of a rebound effect on cessation of treatment. Comparisons of the treatment differences between salmeterol and comparator agent indicated that salmeterol afforded significantly greater protection at all timepoints during treatment, but there was no significant difference during the washout period.

Two of the nine trials measured  $\text{PC}_{20}$  or  $\text{PD}_{20}$  1 h after the first dose, three trials took these measurements between 1 and 12 h after commencing treatment, and eight trials were included in the 'on treatment' phase. Four trials had measurements taken up to 60 h after administration of the last dose, and seven trials more than 60 h after the last dose of drug administration. The overall mean difference in doubling dose between salmeterol and comparator agent, together with 95% confidence limits, for each time interval in the meta-analysis are shown in Fig. 3. These confidence intervals indicate that salmeterol afforded significantly greater protection over the comparator agent at all time points during treatment, with the greatest difference in mean doubling dose being observed up to 1 h after the first administered dose. No significant

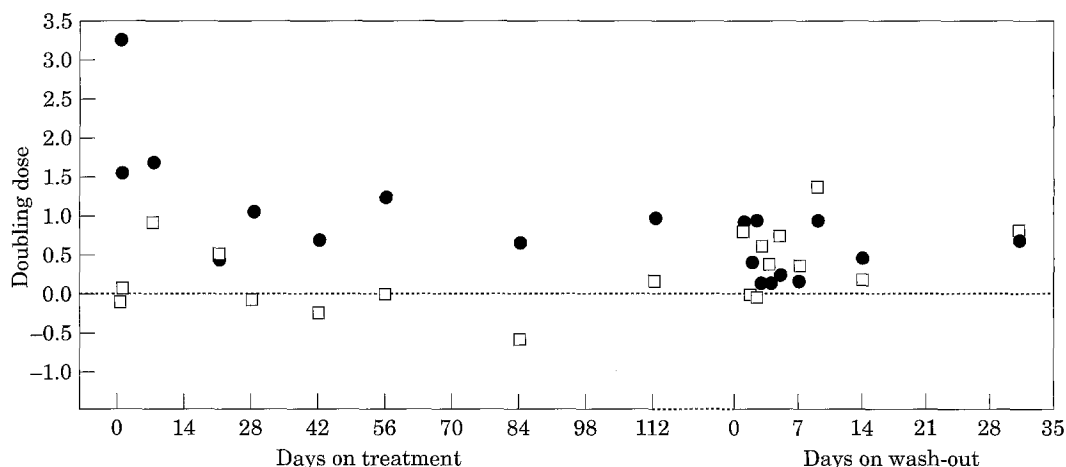


FIG. 2. Combined mean doubling dose values at each time point for salmeterol (●) and comparator (□) drug during treatment and washout periods.

difference in mean doubling dose was observed after stopping trial treatment.

## Discussion

The various clinical trials used in this meta-analysis have all reported that inhaled salmeterol 50  $\mu$ g twice daily maintains its bronchodilator properties during long-term treatment in patients with asthma. However, with regard to its protective effects against bronchoconstrictor stimuli (either inhaled methacholine or histamine), tolerance to the effects of long-term salmeterol have been reported in some (19,23) but not all (17,24) studies. The results of this meta-analysis demonstrate that during long-term regular treatment with salmeterol 50  $\mu$ g twice daily, there is significant, sustained ( $\geq 16$  weeks) protection against histamine- or methacholine-induced bronchoconstriction. The protective effects of salmeterol against a bronchoconstriction were greatest for up to 1 h after the first dose, and any subsequent reduction in this protective effect, which has been

reported in several studies (see 19), was partial and occurred during the first few days of treatment. Overall, the protective effects of salmeterol were maintained throughout treatment. This suggests that in addition to short-term bronchodilatation, salmeterol also affords protection against newly encountered stimuli that can induce bronchoconstriction.

Cheung *et al.* (19) were the first to report the development of tolerance to the bronchoprotective effect of salmeterol against histamine challenge during treatment (50  $\mu$ g twice daily for several weeks); however, the bronchodilator response of salmeterol was maintained. This study showed the bronchoprotective effect of salmeterol decreased from 3.3 doubling doses at 1 h post treatment to 1.0 doubling dose after 4 and 8 weeks of continuous treatment. Other studies have also reported the development of tolerance to salmeterol (18,23–25). In addition, a study examining formoterol, another long-acting  $\beta_2$ -agonist, has indicated that tolerance to the bronchoprotective effect of this drug also occurs during the first few days of treatment (26). The available data suggest that tolerance to salmeterol develops within the first few days of treatment (24), with residual protection against methacholine challenge (1–2 doubling doses) remaining for at least 4 months (23). Co-administration of inhaled corticosteroids does not prevent the development of tolerance (18,25). At present, the clinical relevance of this is not clear.

Following cessation of salmeterol treatment, there was no sustained improvement in airway hyper-responsiveness, as has been observed with inhaled steroids (27–29). However, it should be noted that within the first 60 h following cessation of treatment, there is a tendency towards a protective effect of salmeterol. There has been some concern that regular  $\beta_2$ -agonist monotherapy may result in reduced disease control, especially after stopping treatment (or changing to a non- $\beta_2$ -agonist) (30). However, the results of this study and other (16,19,22) indicate that there is no rebound deterioration in bronchial responsiveness after cessation of salmeterol therapy.

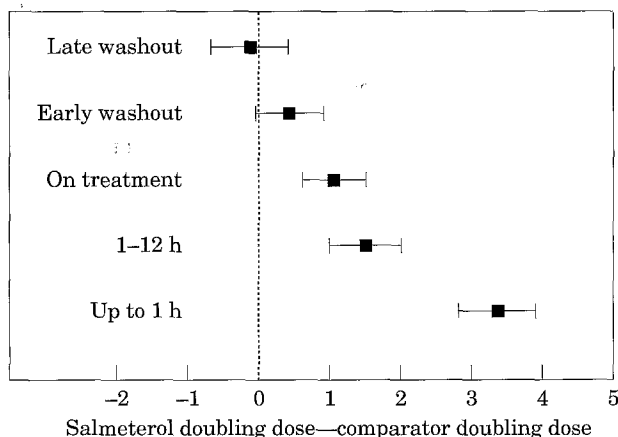


FIG. 3. Mean difference and 95% confidence interval between mean doubling dose of salmeterol and comparator drug at each time interval.

In summary, this meta-analysis suggests that during long-term regular salmeterol treatment, there is significant, sustained bronchial protection over at least 4 months. Any reduction in the protective effect afforded by salmeterol is partial and occurs during the first few days of treatment. In addition, there is no evidence of rebound deterioration in bronchial responsiveness after stopping salmeterol treatment. Thus, salmeterol is a safe and effective treatment for asthma that, in addition to its proven bronchodilator activity, has protective effects against various bronchoconstrictor stimuli.

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